

REMARKS

Applicants acknowledge receipt of the Office Action mailed February 18, 2009 and the Advisory Action mailed July 23, 2009. Claims 10-17 are newly added. Thus, Claims 1-2, 4-8, and 10-17 are pending in the application. Support for new Claims 10-13 can be found, for example, at page 8, lines 11 to 20. Support for new Claims 14-17 can be found, for example, at page 14, lines 2 to 5. Thus, no new matter has been added. Applicants have carefully considered all rejections raised by the Examiner in the Office Action mailed February 18, 2009 and the Advisory Action mailed July 23, 2009 and respond hereto in detail. Reconsideration and withdrawal of the present rejections in view of the amendments and comments presented herein are respectfully requested. In response to the Office Action and Advisory Action, Applicants respectfully request the Examiner to reconsider the above-captioned application in view of the following comments.

Rejection of Claims 1 and 2 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1 and 2 under 35 U.S.C. § 103(a) as being obvious over Liu (Chirality, 12:26-29, 2000) in view of Makarova (Russian Journal of General Chemistry, 71(7):1126-1129, 2001), Gribble *et al.* (Org. Prep. Proc. Int, v. 17, pp. 317-384, 1985), and March (March's Advanced Organic Chemistry, 5th ed., 2001, Wiley, pp. 970-1298).

The Applicants respectfully request the Examiner reconsider the arguments in the reply filed July 14, 2009 in view of the additional comments below.

In particular, Applicants respectfully request the Examiner consider the Declaration of Kenji Kogami under 37 C.F.R. § 1.132 filed on July 17, 2009. The Declaration of Kenji Kogami filed on July 17, 2009 shows that, in the presence of a carboxylic acid, the reduction reaction of the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine proceeds significantly, enabling the production of N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine at a high yield. In contrast, when the reaction is carried out without the presence of the carboxylic acid, the reaction virtually fails to proceed at all. In view of the Declaration, it is clear that this distinction from the prior art is a critical distinction, which could not have been predicted by one having ordinary skill in the art.

The Declaration of Kenji Kogami filed on July 17, 2009 makes clear that it is not predictable that a reduction reaction of any given compound can proceed in the absence of the

proper conditions, such as the carboxylic acid required for the present reaction. Two of the references of record in the present application further support this contention of Applicants.

Gribble Teaches Away from the Claimed Invention

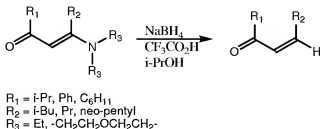
As an initial matter, Applicants wish to note that the Examiner has made a conclusory statement that the teachings of Gribble are directly applicable to applicable to the teachings of Makarova and Liu. The Court has made clear that the Examiner must establish a reason one of skill in the art would have combined the elements of the prior art, and that such reason must be more than a conclusory statement that it would have been obvious.

Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) (“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”). *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007).

The Examiner argues in the Advisory Action that Gribble teaches the use of carboxylic acids in reduction with BH_4 to achieve chemoselectivity, which is directly applicable to Makarova and Liu. The Applicants respectfully request the Examiner specifically point to where Gribble teaches use of carboxylic acids in reduction with BH_4 that are applicable to Makarova and Liu in view of the method of Claims 1 and 2. The Applicants have rigorously reviewed Gribble and are unable to find a supporting teaching as described by the Examiner in relation to the transformation of Claims 1 and 2. In the absence of an explanation, the Examiner provided only a conclusory statement about the applicability of the Gribble reference to the teachings of the other references. Such a conclusory statement does not meet the obligation established by the *KSR* court to set forth articulated reasoning to support the legal conclusion of obviousness.

However, even if it were proper to combine the teachings of Gribble with the other references, doing so would not lead to the presently claimed invention. As noted above, the Applicants are unable to find a supporting teaching as described by the Examiner in relation to the transformation of Claims 1 and 2. However, the Applicants were able to find the reaction of a vinylogous amide in Gribble with NaBH_4 in the presence of a carboxylic acid. Rather than

reducing the vinylogous amide to provide a γ -amino alcohol, this reaction shows elimination of the amino group to provide a vinylogous aldehyde:



. See page 327, Table 3 last entry.

This supports Applicants' argument that the conditions for reduction are not necessarily predictable. Additionally, the chemoselectivity that Gribble teaches is not the same chemoselectivity as provided in Claims 1 and 2. In fact, the conditions recited in the claims lead to an entirely different result in the context of the compounds described by Gribble. Rather than achieving the type of reduction recited in Applicants' claims, the presence of carboxylic acid in Gribble leads to elimination of the amino group to provide a vinylogous aldehyde. In contrast, Applicants' claims require reduction to a γ -amino alcohol, specifically an *N*-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine represented by General Formula (2). Accordingly, based on the teachings of Gribble, a person having ordinary skill in the art desiring to produce a recited compound would conclude that the presence of carboxylic acid is undesirable, as leading to the wrong compound. As such, Gribble teaches away from the claimed invention rather than toward it.

Applicants submit, a *prima facie* showing of obviousness cannot be sustained on the basis of the presently cited references. In direct contradiction to the teaching of Gribble, the Applicants have discovered that the carboxylic acid is critical for the recited reaction to occur. MPEP 2141.02 specifically notes that "a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." In view of the Gribble references teaching away from the invention rather than toward it, the cited combination of references cannot support a *prima facie* showing of obviousness in the absence of a supporting teaching. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this reason.

Bartoli Also Teaches Away from the Claimed Invention

The Examiner acknowledges in the Advisory Action that Bartoli indeed teaches the criticality/difficulty of the reduction. However, the Examiner contends this does not preclude one of ordinary skill in the art from pursuing applications in related contexts. However, based on the teaching of Bartoli one of skill in the art would pursue reduction of vinylogous amides to provide γ -amino alcohol under reducing metal conditions not with NaBH_4 in the presence of acids. See page 537 Scheme 1. Specifically, Bartoli teaches:

(w)e also tried new efficient and powerful reducing systems such as NaBH_4 in the presence of acids (CeCl_3 ,¹⁴ ZnCl_2 ,¹⁵ FeCl_3 ,¹⁶ H_2SO_4 ,¹⁷ etc.) but no appreciable results have been obtained. See page 537, right column, line 3 from the bottom to page 538, left column, line 1.

Thus, Bartoli specifically teaches that the presence of acids lead to “no appreciable results.” Such a teaching is exactly the opposite of what is recited in the presently pending claims, which require the presence of a carboxylic acid. In view of the Bartoli references teaching away from the invention rather than toward it, the cited combination of references cannot support a *prima facie* showing of obviousness in the absence of a supporting teaching. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this reason.

Additionally, Bartoli further supports Applicants’ argument that one of ordinary skill in the art cannot predict the conditions required for reduction of a given a compound. In view of these difficulties, the results reported in the Declaration of Kenji Kogami filed on July 17, 2009 regarding the ability of carboxylic acid to permit the reduction reaction to proceed while no appreciable reaction occurs in the absence of carboxylic acid are truly remarkable and unexpected. These unexpected results further evidence the nonobviousness of the presently claimed invention even in the presence of a *prima facie* showing of obviousness.

Thus, Applicants submit, that for all of the preceding reasons and the reasons set forth in the reply filed July 14, 2009, no proper *prima facie* showing of obviousness of Claims 1 and 2 can be established on the basis of the cited combination of Liu *et al.* in view of Makarova, Gribble *et al.*, and March. Moreover, even if such a showing had been established, the significant unexpected results produced in the presence of carboxylic acid would rebut any such showing. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 4 and 5 under 35 U.S.C. § 103(a)

The Examiner asserts that Claims 4 and 5 are obvious over Liu in view of Makarova. Applicants respectfully traverse the rejection, and request that the Examiner reconsider the arguments in the reply filed July 14, 2009. The Applicant has included select previous arguments for the Examiner's convenience.

The Examiner asserts that Claims 4 and 5 are obvious over Liu *et al.* in view of Makarova. Specifically, the Examiner states as follows:

(i)n addition, one of ordinary skill in the art would immediately recognize how to modify the reaction to produce the claimed invention based on the teachings of Makarova.

However, as explained above, Makarova merely discloses an N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-one, whose structure and chemical characteristics are completely different from those of the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine. Further, Makarova does not disclose the stereochemistry of the N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-one double bond. Thus, Makarova and Liu *et al.* do not teach, alone or in combination, 2-thienyl β -aminovinyl ketones with Z stereochemistry. For at least these reasons Claims 4 and 5 are not obvious over Liu *et al.* in view of Makarova. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this reason.

As discussed previously, the reduction of the N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-one described in Makarova is a particular case, and is attributed to the unique reactivity of the adamantyl group. Therefore, if the adamantyl group of the compound is replaced with another group, the reduction reactivity will be completely changed, which is difficult to predict.

Further, as stated above, even when various β -enamino ketones having a substituent other than adamantyl, such as phenyl, are reacted with a reducing agent, almost no reduction reaction is observed, or nitrogen or oxygen is split from the molecule. The difficulty in reducing the double bond and the oxo group of β -enamino ketones is thus known.

In fact, the reduction of the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine does not effectively proceed in the absence of a carboxylic acid, as discussed in the Declaration of Kenji Kogami filed on July 17, 2009.

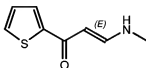
The (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine of the present invention produces the N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine at a high yield when a carboxylic acid is

used as a proton source, this allows the reduction reaction to significantly proceed contrary to when a carboxylic acid is not used as a proton source. In other words, the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine acts as an effective reaction raw material for formation of the N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine in the presence of a carboxylic acid.

Applicants request that the Examiner reconsider the above arguments in view of the additional comments below:

The Claims Are Limited to the Z Isomer

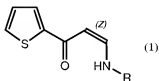
The Examiner has alleged that Claims 4 and 5 read on the following compound:



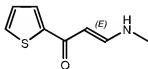
The Examiner's allegation is manifestly incorrect. The Claims do not read on the above structure. The claims are specifically limited to the Z-isomer, while the above compound is the E-isomer. The E-Z nomenclature scheme is recognized by the International Union Of Pure And Applied Chemistry (IUPAC) as designating different stereoisomers involving double binds. The following explanation of the naming of such isomers was established in International Union Of Pure And Applied Chemistry, Organic Chemistry Division Commission On Nomenclature Of Organic Chemistry, Rules For The Nomenclature Of Organic Chemistry, Section E: Stereochemistry, (Recommendations 1974), Collators: L. C. Cross And W. Klyne:

In names of compounds steric relations around one double bond are designated by affixes Z and/or E, assigned as follows: The sequence-rule preferred atom or group attached to one of a doubly bonded pair of atoms is compared with the sequence-rule preferred atom or group attached to the other of that doubly bonded pair of atoms; if the selected pair are on the same side of the reference plane . . . an italic capital letter Z prefix is used; if the selected pair are on opposite sides an italic capital letter E prefix is used.

The Examiner has misinterpreted the structural differences between E and Z isomers of the double bond. Claims 4 and 5 require Z stereochemistry of the double bond as exemplified by (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine represented by General Formula (1):



The structure the Examiner alleges that Claims 4 and 5 read on is an *E* double bond isomer:

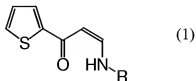


Thus, it is clear that Claims 4 and 5 do not read on the *E* double bond isomer.

Applicants thank the Examiner for providing clarification that the Declaration of Satake Syuzo of November 13, 2008 was fully considered in the Office Action of February 18, 2009. The Applicants respectfully request the Examiner again consider the Declaration of Satake Syuzo of November 13, 2008 in view of the above arguments concerning the differences of *E* and *Z* isomers. As established in the Declaration the two isomers have dramatically different properties. As set forth in MPEP 2141.02, "a compound and all its properties are inseparable." (citing *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963)). In view of the dramatically different properties of the recited isomer from the isomer cited in the Office Action of February 18, 2009, the claims are nonobvious over the cited combination of references.

No Reason to Combine References Has Been Established

Applicants respectfully submit that Liu in view of Makarova do not render the claims *prima facie* obvious. Neither of the references teach a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine represented by General Formula (1):



wherein **R** is C₁₋₄ alkyl as recited in Claim 4.

Nevertheless, the Examiner has suggested combing a moiety of the compounds of Liu with a moiety of the compounds of Makarova could be used to arrive at the current invention. As noted above, the *KSR* decision still requires that some reason for making the combination be present in order to establish a *prima facie* showing of obviousness. The Examiner has not

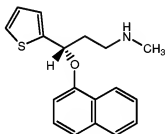
explained any a reason for making such a combination. Rather, in making the combination, the Examiner has simply taken the instant claims and used them as a blueprint to modify the prior art in a piecemeal fashion to arrive at the invention recited in the claims. "It is not proper to dissect claims and reconstruct them in piecemeal fashion by picking and choosing from among the prior art references using the patent as a blueprint. *In re Kamm*, 452 F.2d 1052, 1056-57, 172 USPQ 298, 301-02 (CCPA 1972).

No Reasonable Expectation of Success Has Been Established

Moreover, another requirement for a *prima facie* showing of obviousness is that a reasonable expectation of success be present at arriving at the claimed invention. See M.P.E.P. 2143.02. Even if a reason for combining the references in the manner suggested by the Examiner had been provided, the Examiner has not provided any chemical scheme for producing the claimed compounds that one having ordinary skill in the art could follow with a reasonable expectation of success.

A summary of the teachings of Liu and Makarova are discussed below.

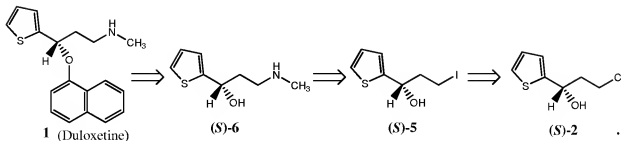
Liu discloses synthesis of enantiomerically enriched:



Duloxetine

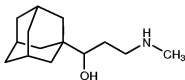
. See pages 27 and 28.

The retrosynthesis of enantiomerically enriched Duloxetine can be seen in Fig. 1:

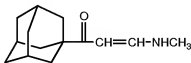


See page 27. It can clearly be seen in the retrosynthesis of Liu *et al.* that no Z-vinyllogous amide intermediates, such as disclosed in Claims 4 and 5, are provided or proposed.

Makarova discloses synthesis of racemic amino alcohols:



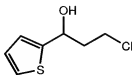
by reduction of an adamantyl vinyllogous amide intermediate:



The Examiner appears to believe that taking the vinyllogous amide from the adamantyl vinyllogous amide intermediate of Makarova and combining it with the thienyl group of Liu would be a trivial task. However, the Examiner has set forth no synthetic scheme for actually carrying out such a reaction or made any other effort to establish that one having ordinary skill in the art would have a reasonable expectation of successfully carrying out such a reaction. Absent such a reasonable expectation of success, no *prima facie* showing of obviousness can be established.

The Combination Renders Liu Unsuitable for Its Intended Purpose

Moreover, combining the intermediates of Liu which are critical for enzymatic resolution with the intermediates of Makarova would render the enzymatic resolution of Liu *et al.* unsatisfactory for its intended purpose. Regardless of the motivation that Liu provides, the intended purpose of Liu is to provide a “Chemo-Enzymatic Synthesis of the Antidepressant Duloxetine and Its Enantiomer.” Thus, the combination of the intermediates of Liu with the intermediates of Makarova would eliminate the key intermediate:



3-chloro-1-(2-thienyl)-1-propanol

and replace it with a vinyl amide group that would be completely unsatisfactory for the intended purpose of Liu. As set forth in M.P.E.P. 2143.01(V) “if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. Thus, for this additional reason, a

proper *prima facie* showing of obviousness cannot be established on the basis of the cited references.

Rejection of Claim 6 under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 6 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* in view of Makarova *et al.*, Wright *et al.* and Guseninov *et al.*

The Applicants respectfully request the Examiner reconsider the arguments in the reply filed July 14, 2009 as discussed below.

The Examiner states that the cited art are relevant due to the method of the amination technique. However, Wright *et al.* teaches a hydroxyamination technique of making vinylogous hydroxamic acids not a technique of making Z-vinylogous amides. The Examiner states that “the Wright reference does teach the same stereochemistry as the claims.” This implies that vinylogous amides and vinylogous hydroxamic acids are structurally the same. This is incorrect. For example, Wright *et al.* teaches a method of making vinylogous hydroxamic acids from E-vinylogous amides. See Method B page 4067. Further, the thienyl examples from Wright *et al.* (Table I entries **2oo** and **2qq**), were synthesized by Method B. The first step of Wright *et al.* Method B provides an E-vinylogous amide which the Examiner must acknowledge is different than a Z vinylogous amide as disclosed in Claim 6. The E-vinylogous amide of Wright *et al.* Method B step 1 is further converted to a vinylogous hydroxamic acid in step 2. Wright *et al.* Method B step 2 does not provide a Z-vinylogous amide as disclosed in Claim 6. Methods A-D, disclosed in Wright *et al.*, all are directed to providing vinylogous hydroxamic acids. Additionally, Wright *et al.* does not disclose using a salt form (e.g. sodium salt) of the β -ketoaldehyde to provide a (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine. Any combination of references with Wright *et al.* would not provide a method of synthesizing a Z-vinylogous amide (e.g. (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine) as disclosed in Claim 6. Thus, the references cannot support a *prima facie* showing of obviousness in the absence of a supporting teaching. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this reason.

As discussed in a previous Office Action response, the Example the Examiner has cited in Guseninov *et al.* discloses formation of an α -chloro- β -aminovinyl ketone where the ketone and the amino group have E stereochemistry in relation to each other. This is in contrast to the

method of Claim 6 which does not include an α -chloro moiety and provides the Z isomer of N-methyl-3-oxo-3-(2-thienyl)propenamine. See Example 1 pages 1-2, Declaration under 37 C.F.R. § 1.132 by Syuzo Satake (November 13, 2008). Additionally, Guseninov *et al.* does not disclose using a salt form (e.g. sodium salt) of the β -ketoaldehyde to provide a (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine. Any combination of references with Guseninov *et al.* would not provide a method of synthesizing a Z-vinylous amide (e.g. (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine) as disclosed in Claim 6. Thus, the references cannot support a *prima facie* showing of obviousness in the absence of a supporting teaching. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this additional reason.

Additionally, any modification of Guseninov *et al.* with Makarova (or any similar method to that disclosed in Makarova) would render Guseninov *et al.* unsuitable for its intended purpose which is formation of an α -chloro- β -aminovinyl ketone where the ketone and the amino group have E stereochemistry in relation to each other. The M.P.E.P states: "(i)f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Accordingly, Applicants respectfully request withdrawal of the rejection for at least this additional reason.

Rejection of Claims 7 and 8 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 7 and 8 under 35 U.S.C. § 103(a) as being obvious over Liu in view of Makarova, Wright *et al.*, Guseninov *et al.*, Gribble *et al.* (Org. Prep. Proc. Int. v. 17, pp. 317-384, 1985), March (March's Advanced Organic Chemistry, 5th ed., 2001, Wiley, pp. 970-1298), and Makarova-2 (Russian Journal of Organic Chemistry, Vol. 37, No. 8, pp. 1099-1101, 2001).

The Applicants respectfully request the Examiner reconsider the arguments in the reply filed July 14, 2009 in view of the additional comments below.

Claims 7 and 8 include the reducing step of Claim 1. Thus, Applicants submit, that for all of the preceding reasons concerning the non-obviousness of Claims 1 and 2 and the reasons set forth in the reply filed July 14, 2009, no proper *prima facie* showing of obviousness of Claims 7 and 8 can be established. The additional cited references do not address the deficiencies of the Liu and Makarova references, and do not teach all limitations of the reduction step. Accordingly,

the cited combination of references cannot support a *prima facie* showing of obviousness in the absence of a supporting teaching concerning the reduction step of Claims 7 and 8.

Moreover, even if such a showing had been established, the significant unexpected results produced in the presence of carboxylic acid would rebut any such showing. Accordingly, Applicants respectfully request withdrawal of the rejection.

Discussion of Obviousness-Type Double Patenting

In the Office Action, the Examiner provisionally rejected Claims 4 and 5 as being objected to under the judicially created doctrine of double patenting as being unpatentable over copending Application No. 11/989,100. In response, Applicants again respectfully request that the issue of obviousness-type double patenting be deferred until such time as either the present application or the co-pending application are in condition for allowance.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Application No.: 10/523,287
Filing Date: February 3, 2005

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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